REMARKS

Claims 1-33 are pending in the application. Claims 8-10 and 16-33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 1-7 and 11-15 have been rejected.

Claims 6, 7, 11 and 15 have been amended and claim 34 has been added. Support for the amendments can be found throughout the specification and the claims as originally filed. Specifically support for down-regulation of SMARCD3 being indicative of prostate cancer can be found throughout the specification (*See*, for example, page 8, lines 4-5 and page 77, lines 31-34). No new matter has been added by the proposed amendments. Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to more particularly point out and distinctly claim the invention to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Restriction

Applicants elect with traverse group 26, claims 1-7 and 11-16, directed to SMARC3. Examiner appears to have changed the claims in group 26 after Applicants' election to exclude claim 16. Applicants believe that this new added restriction is improper and request reconsideration.

Applicants disagree with this restriction imposed by the Examiner in that they split up the SMARC markers of the claimed invention. The screening methods described in claim 16 encompass all SMARC markers disclosed in the application and specifically, SMARC1 and SMARC3 markers. According to the MPEP 803.04, Applicants are entitled to examination of up to ten distinct sequences in a single application without restriction:

> "the Commissioner has decided *sua sponte* to partially waive the requirements of 37 CFR 1.141 *et seq.* and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See *Examination of Patent Applications Containing Nucleotide Sequences,* 1192 O.G. 68 (November 19, 1996). It has been determined that normally ten sequences constitute a

> reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction." (Emphasis added.)

In addition, Bruce A. Lehman, Assistant Secretary of Commerce and Commissioner of Patents and Trademarks, clarified the PTO's policy for examination of patent applications that claim large numbers of nucleotide sequences in his Notice entitled "Examination of Patent Applications Containing Nucleotide Sequences" (October 17, 1996, 1192 OG 68). The Notice elaborated on the PTO's policy of *not* restricting combination of nucleotide sequences:

> "Applications claiming only a combination of nucleotide sequences ... will generally ***not*** be subject to a restriction requirement. The presence of one novel and nonobvious sequence within the combination will render the entire combination allowable. The combination will be searched until one nucleotide sequence is found to be allowable. The order of searching will be chosen by the examiner to maximize the identification of an allowable sequence." (Emphasis added.)

Thus, Applicants urge the Examiner to amend restriction group 26 to include claim 16 as originally set forth in the restriction requirement mailed July 29, 2003.

Objection

The Examiner objects to claims 1-7 and 11-15 because part of claims 1-7 and 11-15 are drawn to a non-elected invention. Applicants respectfully disagree with the basis for this objection.

Applicants see no reason to amend the claims to impose limitations that were not part of the claims as originally filed. Furthermore, claim 1 is a generic linking claim directed to the SMARC markers that exhibit an altered expression associated with prostate cancer as conceded by the Examiner. Thus, upon allowance of a linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn with regard to any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s). In addition, the phrase "comprising detecting a difference in **protein level** of expression of SMARC markers" does not appear in claims 1-7 and 11-15 as the Examiner states. Applicants urge the Examiner to reconsider this objection in light of these remarks.

Claim Rejection Under 35 U.S.C. § 101

Claims 1-7 and 11-15 are rejected under 35 U.S.C. § 101 because the Examiner states that the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility. Applicants disagree with the basis of this rejection and respectfully request reconsideration in light of the following remarks.

The Examiner states that there is "no data showing actual detection of any differential expression of SMARCD-3 in prostate tumor as compared to normal prostate tissue." Furthermore, the Examiner states that "one cannot determine that SMARCD3 would have differential expression in prostate cancer as compared to normal tissue."

In response, Applicants respectfully direct the Examiner to the teaching of the Applicants' Specification in which the application clearly states that the SMARC genes were initially identified using Affymetrix Genechip™ technology as being *significantly, differentially expressed* in diseased cells *when compared to normal cells* (*See* for example, Specification page 7, lines 29-31 and page 78, lines 4-6). Furthermore, expression of the prostate specific antigen (PSA) gene, which has been extensively studied as a biomarker in prostate cancer and has proven to be predictive of clinical responses in prostate cancer patients to therapy, was used as an internal control in the experiments disclosed in the application (*See* page 8, lines 6-9 of the Specification). The correlation between the decreased expression of SMARCD3 and increased expression of the prostate cancer biomarker PSA further indicates that SMARC genes are associated with prostate cancer.

Moreover, Applicants point out that LNCaP is a well-characterized cell line that has been widely used in the study of prostate cancer. The growth and maintenance of prostate cancer cells are often dependent on androgen (*See* Background). The androgen-responsive feature of LNCaP makes it a useful *in vitro* model for the study of regulation of prostate related genes since the expression of many prostate-specific proteins require functionally differentiated, androgen-responsive cells. Those skilled in the art view LNCaP cells as an established *in vitro* model of prostate cancer.

The Examiner states that the disclosed method is based on 6000 genes, which is under-represented of all mRNAs in a cell and that "[i]t is known that cells in the human body seem to have approximately 100,000 genes." The Applicants disagree with the basis of the Examiner's rejection and also with the Examiner's estimate of the number of known genes.

Today's estimate of the number of known genes is much lower than the previous estimates of around 100,000, which were quoted by the Examiner. The initial analysis of the draft human genome sequence, which was published by the International Human Genome Sequencing Consortium on February 15, 2001, estimated only about 30,000 to 40,000 protein-coding genes. However, more recent estimates from gene-prediction programs suggest that there might be 24,500 or fewer protein-coding genes (Elizabeth Pennisi. "A Low Number Wins the GeneSweep Pool." *Science* 300, 1484 (2003); Jean-Michel Claverie. "Gene Number. What If There Are Only 30,000 Human Genes?" *Science* 291, 1255–7 (2001)). Nonetheless, Applicants do not see why the number of genes in the human body is relevant to the present invention. Applicants have identified a group of markers, SMARC markers, that are *significantly, differentially expressed* in diseased cells *when compared to normal cells*.

According to MPEP 2107.02, a rejection based on lack of utility is not to be made if the applicant has asserted that the claimed invention is useful for any particular purpose and this assertion would be considered credible by a person of ordinary skill in the art, in view of all the evidence of record, or if the invention has a well established utility wherein a person of ordinary skill in the art would immediately appreciate why the invention is useful. Applicants demonstrated that SMARCD3 yielded a statistically significant ($p<0.05$) difference between the diseased and normal tissues in a screen of 6800 known genes for expression in androgen dependent prostate cancer cells (See Specification, page 7, line 31-32). In addition, the correlation between the decreased expression of SMARCD3 and increased expression of the prostate cancer biomarker PSA further indicates that SMARC genes are associated with prostate cancer. Furthermore, Applicants used LNCaP cells, which are viewed by those skilled in the art view as an established *in vitro* model of prostate cancer. In light of all the evidence presented in the application, Applicants respectively request that the Examiner withdraw the utility rejection.

Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-7, 11-15 are rejected under 35 U.S.C 112, first paragraph. Applicants respectfully traverse this rejection. In light of the following amendments and remarks, Applicants respectfully request that this rejection be withdrawn.

The Examiner asserts that claims 1-7 and 11-15 lack enablement since the claimed invention is not supported by a well established utility. This rejection is obviated by Applicants' above arguments. In particular, Applicants have established utility for the above invention in the screening and diagnosis of prostate cancer by demonstrating that SMARCD3 yielded a statistically significant ($p<0.05$) difference between the diseased and normal tissues and that a correlation between the decreased expression of SMARCD3 and increased expression of the prostate cancer biomarker PSA.

The Examiner states that one cannot extrapolate the teaching in the specification to the enablement of claims 1-7 and 11-15 because one would not know how to make the invention, due to the lack of disclosure in the claims and in the specification of the actual sequence of SMARCD-3. The Examiner asserts that the Applicant is required to amend the disclosure to include the sequence that was incorporated by reference. In response, Applicants have amended page 73 of the specification and submit herewith a revised sequence listing including the sequences of both SMARCD1 and SMARCD3 as SEQ ID NO: 4 and SEQ ID NO: 5, respectively. In addition, Applicants also submit herewith a Statement from the Applicants' representative stating that the amendatory material consists of the same material incorporated by reference, as required by the Examiner.

The Examiner states that a difference in the mRNA level of SMARCD3 in prostate cancer tissue compared to normal prostate tissue in claims 1-7 and 11-15 encompasses either an increase or a decrease of the mRNA level. In response to the Examiner's statements, Applicants have amended claims 6 and 7 to reflect that down-regulation of SMARCD3 is indicative of prostate cancer, as disclosed in the invention. Specifically, the amended claims 6 and 7 recite that the level of expression of SMARCD3 in the sample "is lower than" the normal level of

expression of SMARCD3 in a subject not afflicted with prostate cancer by a factor of about at least 2 or 3, respectively.

The Examiner's states that "one cannot predict whether said difference is by a factor of about at least 2 or above at least 3, which reads on a range of any number of factors as long as they are above 2 or 3, for example, 1000 fold difference." Applicants do not understand the basis of the Examiner's rejection.

As amended, Applicants claim that SMARCD3 is decreased from the normal level by a factor of about at least 2 or 3. Applicants' invention associates a down-regulation in the level of SMARCD3 with prostate cancer. Thus, any decrease above a factor of about 2 in the level of SMARCD3 is associated with prostate cancer and falls within the scope of Applicants' invention. Applicants do not require that "one *predict* whether there is a difference in mRNA level of SMARCD-3 in prostate cancer tissue" as stated by the Examiner. In contrast, Applicants' specification is replete with experimental ways of objectively determining the expression level of SMARCD3 (*See*, for example, Specification page 9, line 3 to page 11, line 7, page 22, lines 8-19, Page 73, lines 1-28, and page 78-79 (Example 3: Detection of SMARC Markers)). Accordingly, the Examiner is respectfully requested to reconsider this rejection.

The Examiner also rejects claims 1-3, 6-7, and 11-15 since "one cannot *predict* whether there is a difference in mRNA level of SMARCD-3....one cannot predict whether cells from any tissue to which prostate cancer has metastasized, or metastasized prostate cells would still over- or under-express SMARCD-3." Applicants disagree with the basis of this rejection in light of the claim amendments and remarks above.

Applicants invention does not require *prediction* of either a difference in mRNA levels of SMARCD3 or a *prediction* of "whether cells from any tissue to which prostate cancer has metastasized" as the Examiner states. As discussed above, Applicants' invention associates a decrease in SMARCD3 expression with prostate cancer and provides examples of how to test for such a decrease in expression.

The Examiner further states the "it is well known in the art that expression of a sequence could be lost during the progression towards metastasis." Applicants do not see how this is

relevant to the claimed invention. Applicants' invention associates, for example, a decrease in SMARCD3 expression with prostate cancer. If a subject's cells that normally express SMARCD3 at a certain level are found to have a decrease in expression, the present invention would identify that subject. If there is no change in the expression of SMARCD3, the subject would not be identified.

The Examiner also states that "in absence of objective evidence that there is a difference in mRNA level of SMARCD-3 in prostate cancer tissue as compared to normal prostate tissue....one of skill in the art would be forced into undue experimentation to practice the claimed invention." Applicants respectfully disagree with this rejection. As discussed above, the application clearly states that the SMARC genes were identified using Affymetrix Genechip™ technology as being *significantly, differentially expressed* in diseased cells *when compared to normal cells* (*See* for example, Specification page 8, lines 17-23). In addition, Applicants Specification teaches that SMARCD3 expression levels are decreased in cells associated with prostate cancer (See, Specification page 77, lines 31-34). Furthermore, expression of the prostate specific antigen (PSA) gene, which has been extensively studied as a biomarker in prostate cancer and has proven to be predictive of clinical responses in prostate cancer patients to therapy, was used as an internal control in the experiments disclosed in the application (*See* page 8, lines 6-9 of the Specification). The correlation between the decreased expression of SMARCD3 and increased expression of the prostate cancer biomarker PSA further indicates that SMARC genes are associated with prostate cancer. In light of the teaching of the specification, the Examiner is requested to withdraw this rejection.

The Examiner rejects claims 11-14 due to "the language 'a' transcribed polynucleotide in claim 11" since the claim would encompass "any unrelated" transcribed polynucleotide. In response, Applicants have amended claim 11 to recite "a transcribed polynucleotide or portion thereof *corresponding to said marker*." Accordingly, the Examiner is respectfully requested to withdraw this rejection.

The Examiner also rejects claim 15 for encompasses "detecting unrelated polynucleotide or portion thereof." In response, Applicants have amended claim 15 to recite "detecting the

presence in said sample of a transcribed polynucleotide, or portion thereof, *corresponding to said marker*." Accordingly, the Examiner is respectfully requested to withdraw this rejection.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. In the event that the amendments and remarks are not deemed to overcome the grounds for rejection, the Examiner is kindly requested to telephone the undersigned representative to discuss any remaining issues.

Respectfully submitted,

NUTTER, McCLENNEN & FISH, LLP

Date: April 29, 2004

Thomas J. Engellenner
Registration No.: 28,711
Attorney for Applicants
World Trade Center West
155 Seaport Boulevard
Boston, MA 02210-2604
Tel: (617) 439-2948
Fax: (617) 310-9948

1316878.1